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ORIGINAL ARTICLE

D-dimer testing cannot rule out thromboembolism after major lower extremity arthroplasties and thromboprophylaxis treatment

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Abstract
Purpose Our previous study showed, for the first time, that a guideline-recommended thromboprophylactic strategy reduced the prevalence of venous thromboembolism (VTE) including venous thromboembolism and pulmonary embolism after arthroplasties of the major lower extremities, such as total hip arthroplasty (THA) or total or partial knee arthroplasty (TPKA), to 4.4 %. In this retrospective study, we examined the diagnostic value of D-dimer for VTE and try to confirm the low prevalence of VTE after THA or TPKA.
Methods This was a retrospective study including 380 procedures of 361 patients who underwent elective 129 TPKA or 251 THA, as well as multidetector computed tomography (MDCT) on postoperative day 7 with D-timer testing to screen for VTE. In 303 of 380 procedures, D-timer testing was performed on the same day as MDCT. The antithrombotic prophylaxes included medical and mechanical therapy and early ambulation.
Results The prevalence of VTE was 4.5 % (17 cases) (95 % confidence interval 2.4−6.6 %). The D-dimer level was significantly greater in patients with VTE than in those without (13.4 ± 11.1 vs 10.1 ± 6.5 μg/mL). At the lowest cut-off value of 4.0 μg/mL, D-dimer testing ruled out VTE in only 26 of 303 cases with 1 (6 %) false negative result.
Conclusions The low incidence of postoperative VTE with the strict anticoagulation strategy was confirmed in this validation study. D-dimer testing is not useful for excluding VTE postoperatively in patients who undergo THA or TPKA.

Keywords D-dimer · Pulmonary embolism · Total hip arthroplasty · Total knee arthroplasty · Multidetector computed tomography

Introduction

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are the most serious complications in patients after major lower extremity arthroplasties, including total hip arthroplasty (THA) or total or partial knee arthroplasty (TPKA). These complications occur in 51 % and 40−60 % of patients, not treated with prophylaxis, after TPKA [1] and after major extremity arthroplasties [2], respectively. Previously, we demonstrated for the first time that a guideline-recommended thromboprophylactic strategy reduced the prevalence of venous thromboembolism (VTE), including DVT and PE, after total hip or total or partial knee arthroplasty (THKA) to 4.4 % in a study enrolling 1,163 cases screened with comprehensive multidetector computed tomography (MDCT) [3, 4]. This low prevalence had not been previously reported in a study enrolling >100 patients. In addition, we found there was a significant difference in D-dimer levels one week after surgery between patients with and without VTE, suggesting that the D-dimer level may be used to exclude VTE after THKA. In an outpatient group with a low clinical probability for PE, there was a 9 % prevalence of PE, which is substantially higher than the postoperative patients undergoing THKA in our cohort

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[4, 5]. The two aims of this study were (1) to confirm the low prevalence of VTE in another cohort treated with the same guideline-recommended thromboprophylaxis after TPKA or THA and (2) to examine the diagnostic value of D-dimer to rule out VTE in postoperative patients.

Methods

We reviewed the patient records from July 2013 to June 2014 at our institution and found 438 elective arthroplasties, TPKA and THA that had been performed during this period. Fifty-eight procedures were excluded from the analysis because they did not undergo MDCT. The remaining 380 procedures (males: 61, females: 319) were included and analyzed (Fig. 1). The antithrombotic prophylaxis was reported elsewhere [3, 6]. Briefly, patients received one of the following anticoagulation regimens—enoxaparin, 20 mg twice a day; fondaparinux, 15 mg once a day; or intravenous heparin for 7 days beginning 24 h after surgery, if there were no contraindications. Patients wore pneumatic compression devices and compression stockings until ambulation.

The patients underwent MDCT pulmonary arteriography and venography as comprehensive screening for the diagnoses of PE and DVT, respectively, on postoperative day 7. The techniques and protocol for performing MDCT are described elsewhere [3]. D-dimer was also measured on the same day as the MDCT using latex agglutination turbidimetry (CS-5100; Sysmex, Kobe, Japan). Staff radiologists interpreted the MDCTs as usual. When the diagnosis of VTE was not conclusive on the MDCT, mostly when there was suspected DVT in the distal veins, the diagnosis was made with venous compression ultrasonography (US) of the lower extremities. The patients were divided, according to the diagnosis, to either the VTE positive (+) or VTE negative (–) group.

Statistics

Data are presented as mean ± SD. Data were assessed per procedure rather than per patient because some of the patients underwent the same procedures on the other side or a revision in this period. Data were analyzed using Microsoft Excel (2007). 95 % confidence interval (CI) for proportions was estimated based on the binomial distribution. We used the *T* test to compare the prevalence of VTE between the current and the previous studies and the D-dimer levels of the two cohorts, i.e., patients with or without VTE. The sensitivity, specificity and negative predictive value were calculated at varying cut-off D-dimer levels. ROC analysis was used to calculate the best cut-off D-dimer level. A p value <0.05 was considered statistically significant.

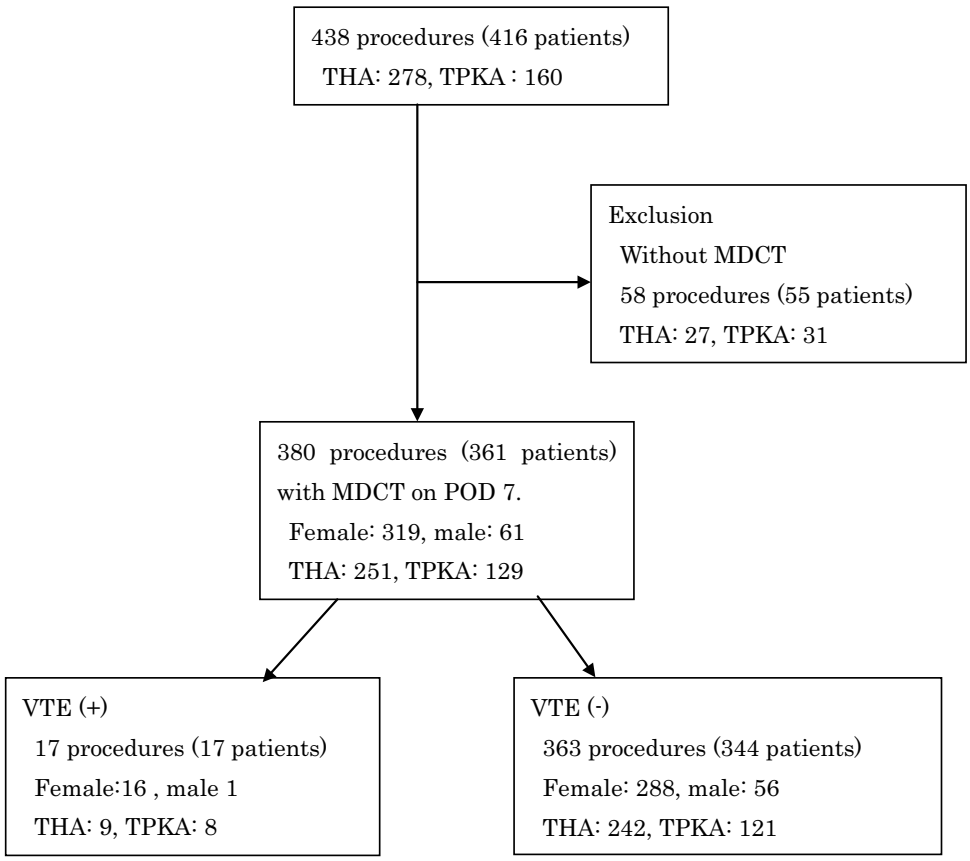

Fig. 1 Flow chart of the study. Because some patients underwent more than one surgery for revision or arthroplasty of the other side, the number of patients and procedures are presented. *MDCT* multidetector computer tomography, *POD* postoperative day, *THA* total hip arthroplasty, *TPKA* total or partinal knee arthroplasty, *VTE* (+) patients with venous thromboembolism, *VTE* (–) patients without venous thromboembolism

Results

A total of 416 patients underwent 438 THKA (278 THR, 160 TPKA) procedures. Among them, 361 patients underwent 380 THKA (251 THR, 129 TPKA) as well as MDCT on postoperative day 7. Patient characteristics are summarized in Table 1. There were 17 (males 2, females 15) cases diagnosed with VTE (8 PE, 13 DVT and 4 PE + DVT) using MDCT. The prevalence of VTE in the current study (4.5 %, 95 %CI 2.4−6.6 %) was consistent with our previous study (4.4 %) [3]. No patient suffered from major bleeding or death after THKA.

Table 1 Characteristics of the study patients who underwent MDCT for VTE after surgery

	Total procedures ($N = 380$)
Patients	361
Age, years	70 ± 11
Female gender, *n* (%)	319 (84)
Weight, kg	57 ± 11
Height, cm	153 ± 8
BMI, $kg \cdot m^{-2}$	25 ± 4
Types of arthroplasty	
TPKA, *n* (%)	129 (34)
THA, *n* (%)	251 (66)
Anticoagulants	
Enoxaparin, *n* (%)	201 (53)
Fondaparinux, *n* (%)	78 (21)
Heparin, *n* (%)	6 (2)
No medication, *n* (%)	95 (25)
Duration of hospitalization, days	25 ± 15
Mortality, *n* (%)	0 (0)
Major bleeding, *n* (%)	0 (0)

Data were assessed per procedure rather than per patient, except for the number of patients. Means ± SD are reported. *MDCT* multidetector computed tomography, *BMI* body mass index, *POD* postoperative day, *THA* total hip arthroplasty, *TPKA* total or partial knee arthroplasty, *VTE* venous thromboembolism

The D-dimer was measured in 303 cases on the same day as the MDCT. The D-dimer levels were significantly different (13.4 ± 11.1 and 10.1 ± 6.5 μg/mL for DVT (+) and DVT (–) cases, respectively) between the two groups ($p < 0.05$). ROC analysis showed that the AUC was 0.59, indicating a moderate predicting value. The best cut-off level of D-dimer was 8.5 μg/mL which had 76 % (95 %CI 56−96 %) sensitivity, 45 % (95 %CI 39−51 %) specificity, and a 97 % (95 %CI 94−100 %) negative predictive value for the diagnosis of VTE. The number of cases within the cut-off was 134 (44 %). The test values at varying cut-off levels of D-dimer are shown in Table 2. Increasing cut-off levels decreased the sensitivity and negative predictive values. When adopting a cut-off value of 4.0 μg/mL, D-dimer testing could rule out VTE in only 26 of 303 cases with 1 (6 %) false negative result.

Discussion

We analyzed the prevalence of postoperative VTE after THKA in a retrospective study of patients who had undergone comprehensive MDCT screening at our institution. The VTE prevalence was 4.5 % (95 %CI 2.4−6.6 %), the same as our previous study, and we did not find a safe D-dimer cut-off level to rule out VTE in patients postoperatively after THKA; although, the mean D-dimer levels differed between patients with and without VTE. An increased postoperative D-dimer level is well recognized [4, 5, 7]. Shiota et al. [5] found that a cut-off level of 10 μg/mL on postoperative day 7 is an indication of DVT. The value is similar to our cut-off level indicated by the ROC analysis. The D-dimer level increased in a sinusoidal pattern, with an initial peak at 12 h and secondary peak on postoperative day 7 in patients with THKA; therefore, we determined the D-dimer level on postoperative day 7.

Table 2 Effects of varying cut-off levels of D-dimer on test characteristics in postoperative patients

D-dimer cut-off level, μg/mL	Sensitivity % (95 % CI)	Specificity % (95 %CI)	Negative predictive value % (95 %CI)	D-dimer below cut-off level, no. of cases (%)
2.0	100	0	100	0
3.0	100	3 (1−5)	100	10 (3)
4.0	94 (83−100)	9 (6−12)	96 (89−100)	27 (9)
5.0	82 (64−100)	15 (11−19)	93 (86−100)	45 (15)
6.0	76 (56−96)	22 (18−27)	94 (88−100)	67 (22)
8.5	76 (56−96)	45 (39−51)	97 (94−100)	134 (44)

The test values at varying cut-off levels of D-dimer are shown. Increasing cut-off levels decreased the sensitivity and negative predictive values, while specificity increased. The best cut-off level of D-dimer was 8.5 μg/mL, which had 76 % sensitivity, 45 % specificity, and a 97 % negative predictive value for the diagnosis of VTE. *CI* confidence interval, *VTE* venous thromboembolism

In non-surgical outpatient settings, patients suspected as having PE are first evaluated according to the clinical probability assessment. If they are categorized to a low clinical probability group, the D-dimer test can rule out PE. In our cohort, the prevalence of VTE was 4.5 %, while the prevalence of PE was 1.7 %. These values are similar to those of a low clinical probability group. Thus, we evaluated the usefulness of D-dimer testing in postoperative patients who underwent THKA. To use D-dimer testing to rule out VTE in the postoperative patients, the sensitivity and negative predictive value must be nearly 100 %, with a meaningful number of negative samples, as was the case for the diagnosis of PE in suspected outpatients. However, we could not find a safe cut-off level of D-dimer to exclude VTE in postoperative patients with good sensitivity and a negative predictive value, even though the prevalence of VTE in our cohort was as low as in the low clinical probability group of outpatients. In contrast to the low clinical probability outpatients, where the D-dimer level was <1.0 μg/mL in most patients, the distribution of D-dimer levels in the postoperative patients was greater, as indicated by the SD values of 11.1 and 6.5 for the VTE (+) and VTE (–) groups, respectively.

The current study confirmed the low prevalence of VTE after THKA with guideline-recommended antithrombotic prophylaxis. The diagnostic sensitivity for VTE depends on the imaging modality and the examiner's skills. Although the diagnosis of VTE was inconclusive with MDCT, as US was necessary for a definitive diagnosis, we think MDCT is the most reliable and examiner-independent modality for the diagnosis and later management of VTE. Although concealed VTEs, especially in the calf vein or in the distal pulmonary vein, could not be clearly diagnosed on MDCT, it is unclear whether such patients should be treated with anticoagulants. The absence of VTE-related mortality and morbidity in the current and previous studies [3], including >1,500 patients, emphasizes the appropriateness of diagnosing VTE using MDCT and the subsequent anticoagulant treatment of patients with VTE.

In conclusion, the low incidence of postoperative VTE (4.5 %, 95 %CI 2.4−6.6 %) in patients treated with a strict anticoagulation strategy was confirmed in this validation study. Although, the D-dimer level on the postoperative day 7 was greater in the VTE (+) group than that in the VTE (–) group, we did not find that D-dimer testing was useful for the diagnosis of VTE in patients after THKA.

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